Annex 1 / Page 1

INDUSTRIAL FARMACEUTICA CANTABRIA, S.A.

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Arequipa, 1.
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E Mail: carlos.perez@ifc.es

Nº 00974650664	A/To:
Páginas/Pages: 1	Att: NIDA NASSIEF
Fecha/Date: 18/04/02	De/From: CARLOS PEREZ

Dear Abdul-Ghani Nida Nassief,

I would like you to know that IFC is interested in opening new markets for its product (Glicofosfopeptical) in the Middle East.
As you know perfectly well our future partner, who will distribute the product, should show to us the strategy plan to sell it in the territory agreed. It so to say that IFC should know (before giving its product) the possibilities of the partner to distribute properly our product, therefore is absolutely need to know its Marketing plan and the forecast for the first two or three years.

We know that you have done a hard scientific work with our Glicofosfopeptical concentrating your effort in the Asthma treatment. In this respect we also know yours applications about Britain patent Nº 2348132 (dated 01/03/2000) and International patent of PCT/IB00/00222 (dated 02/03/2000) both of them with the same claims wherein you appear as inventor.

According to Mr. Juan Matil told to Dr. Sattar in our offices, IFC would like to offer you the following possibilities to reach a distribution agreement:

Alternative I (SUPPLY AGREEMENT)

IFC would reach a semi-exclusivity agreement to sell to you the raw material (Glicofosfopeptical) as long as you manufacturing the finished product with our Glicofosfopeptical alone or with another ingredients in order to sell it under your own trademark as nutriceutical or herbal medicine product in the territory agreed.

You shall permit IFC to visit your factory in order to check whether the product is being manufactured properly, thus IFC will assign qualified members of its technical staff to do it.

In the case of you will be able to buy us more than 250.000 $ USD during the first two years this contract will be of exclusivity.

Alternative II (DISTRIBUTION AGREEMENT)

IFC would reach an exclusivity agreement to sell to you finished product (Glicofosfopeptical) as long as you sell it under our own trademark (Inmunoferon or whatever IFC decides) within territory agreed.

You shall recognise the exclusive ownership by IFC as proprietary related of the product (both Pharmaceutical register and trademark). Also you shall be agree not to make any type of use or engage into any claim on the trademark or any other proprietary right related to the product and further agrees to respect IFC proprietary rights on them.

I am looking forward to receiving your business plan soon
Kindest regards

Carlos Perez
International Manager

Anex 1 /p 2

From: "Diracdh_General" <direccciongeneral@andromaco.com.mx> | **Add to Address Book**
To: nidasthma@yahoo.com
Subject:
Date: Fri, 15 Aug 2003 15:37:07 -0500

Dear Dr. Nasif:

Sending medicines from México to another country by international courrier like UPS is not easy.

We have decided to send the samples of our product INMUNOL /Glicophosphopeptical) by registered mail.

I gave to a Canadian friend, who was visiting us, some samples to send by mail from Canada.

Let me know if you received them correctly and if you find that they give you the same results as INMUNOFERON.

In a few days, I will send you the letter you asked for.

Best wishes,
Enrique Rubí

Annex I / P3

This message is not flagged. [Flag Message - Mark as Unread]

From: "Direccih_General" <direcciongeneral@andromaco.com.mx> [Add to Address Book
To: nidasthma@yahoo.com
Subject:
Date: Wed, 3 Sep 2003 13:18:09 -0500

Dear Dr. Nasif:

I expect that by now you should have received by registered mail 90 capsules of INMUNOL from Mexico and another 90 capsulas from Canada.

Yes, we do have some published research (in Spanish) but not on asthma.

Please confirm reception and let me know if you obtained the same results than the Spanish product.

As far as the letter is concerned, could you send me the text.

Thank.

Best regards,
Enrique Rubi

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Annex 2

January 26, 1998

Nida A-G Nassief, M.D.
P.O. Box 4095
Al-Mahatta
Amman 1131
JORDAN

Dear Dr. Nassief:

Thank you for your packet of information to the Food and Drug Administration (FDA). Your information has been forwarded to the Center for Drug Evaluation and Research (CDER), part of the FDA, for response.

In your letter, you ask the agency to assess the research you enclosed regarding asthma management. In order for a drug to be approved for a new indication, it would have to be submitted to the FDA for review as a New Drug Application (NDA). I will forward your name and address to our Office of Drug Information, who will send you an NDA packet and instructions under separate cover.

The FDA does not patent products, so you may wish to contact the Patent and Trademark Office at (800)786-9199.

I hope this information is useful. If I can provide future assistance, please do not hesitate to contact me.

Sincerely,

Liz Ortuzar
Executive Secretariat Team, HFD-006
Center for Drug Evaluation and Research

Annex 3 P1

A. The Utility Requirement Requires that a Claimed Invention Hav a Specific "Usefulness" with "Real World" Value

To satisfy § 101, an invention must be "useful."[1] Courts have used the labels "practical utility" or "specific utility" to refer to this aspect of the "useful invention" requirement of § 101. As the Court of Customs and Patent Appeals stated in Nelson v. Bowler:

> "Practical utility" is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public.[1]

Practical considerations require the Office to rely on the inventor's understanding of his or her invention in determining whether and in what regard an invention is believed to be "useful." Because of this, Office personnel should focus on and be receptive to specific assertions made by the applicant that an invention is "useful" for a particular reason. Office personnel should distinguish between situations an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful.[4] Assertions falling within the former category are sufficient to identify a specific utility for the invention.

Assertions that fall in the latter category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant.[5]

Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific utility based on the setting in which the invention is to be used. Inventions that are to be used exclusively in a research setting (i.e., "research tools") illustrate the problem. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific utility for the invention.

Office personnel also must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases[6] to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "specific" utility.

B. Wholly Inoperative Inventions Are Not "Useful" Inventions Under 35 U.S.C. § 101; "Incredible" Utility

An invention that is "inoperative" (i.e., it does not operate to produce the results claimed by the patent applicant) is not a "useful" invention in the meaning of the

Annex 3 P2

C. Therapeutic or Pharmacological Utility

Inventions asserted to have utility in the treatment of human or animal disorders are subject to the same legal requirements for utility as inventions in any other field of technology.[19] As such, pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy § 101.[20]

Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and thus satisfies the utility requirement.[21] As the CCPA held in Nelson v. Bowler:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.[22]

Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition.[23] Accordingly, Office personnel should not construe § 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans.[24]

These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear--the invention is asserted to be useful in treating the particular disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under § 101.

D. Relationship Between § 112, First Paragraph, and § 101

A deficiency under § 101 also creates a deficiency under § 112, first paragraph.[25] For example, the Federal Circuit recently noted, "[o]bviously, if a claimed invention does not have utility, the specification cannot enable one to use it."[26] As such, a rejection properly imposed under § 101 should be accompanied with a rejection under § 112, first paragraph. It is equally clear that a rejection based on "lack of utility," whether grounded upon § 101 or § 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible). To avoid confusion, any rejection that is imposed on the basis of § 101 should be accompanied by a rejection based on § 112, first paragraph. The § 112, first paragraph, rejection should be set out as a separate rejection that incorporates by reference the factual basis and conclusions set forth in the § 101 rejection. The § 112, first paragraph, rejection should indicate that because the invention as claimed does not have utility, a person skilled in the art would not be able to use the invention as claimed, and as such, the claim is defective under § 112, first paragraph. A § 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under § 101 under these guidelines.[27] In p rticular, the factual showing needed to impose a rejection under § 101 as outlined in these guidelines must be provided if a rejection based on § 112, first paragraph, is to be imposed on "lack of utility" grounds.

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asthma by degranulating and releasing mediators such as histamine, bradykinin, chemotactic factors, platelet-activating factor, and metabolites of arachidonic acid such as prostaglandins and leukotrienes. Neural factors may augment this response. These mediators act locally to effect bronchoconstriction, cellular infiltration, platelet activation, increased vascular permeability, edema, and increased secretion of mucus. Besides mast cells, other lung cells, including eosinophils, neutrophils, and lymphocytes, play important roles in the immunopathogenesis of airways inflammation in asthma. Airway narrowing in asthma results from a combination of smooth muscle spasm, airway edema and inflammation, and mucus plugging. Successful therapy depends upon reversing each of these factors.

Exercise-induced asthma occurs 5–10 minutes after the patient starts to exercise and may be related to heat loss or water loss from the bronchial surface. Triad asthma, a combination of asthma, aspirin sensitivity, and nasal polyposis, occurs in fewer than 10% of asthma patients. Bronchoconstriction in this condition is due to the effects on arachidonic acid metabolism of aspirin and other nonsteroidal anti-inflammatory agents, tartrazine dyes, and other compounds. Occupational asthma may be triggered by various agents found in the workplace and occurs a few weeks to many years after initial exposure to an offending agent. Nocturnal cough may be the only symptom. Cardiac asthma represents bronchospasm precipitated by congestive heart failure, probably as a result of vasodilation of blood vessels in small airways. Asthmatic bronchitis denotes chronic bronchitis with features of bronchospasm that quickly responds to bronchodilator therapy. Drug-induced asthma is caused by many commonly used agents (Table 9–24).

Clinical Findings

A. Symptoms and Signs: Asthma is characterized by episodic wheezing, feelings of tightness in the chest, dyspnea, and cough. The frequency of asthma attacks is highly variable. Some patients may have very infrequent, brief attacks of asthma; others may suffer nearly continuous symptoms. Asthma is often worse at night. Nocturnal asthma is usually most severe around 3–4 AM, when circadian variations in bronchomotor tone and bronchial reactivity result in bronchoconstriction.

Asthma attacks occur spontaneously or result from various "trigger factors," including nonspecific irritants (dusts, odors, cold air, sulfur dioxide fumes), emotional stress, upper respiratory infections, sinusitis and postnasal drip, exertion, exposure to aeroallergens, aspiration, and abrupt changes in weather. The antigens of the ubiquitous house dust mite represent an important aeroallergen for many patients with asthma. Inhalation of aeroallergens often initiates wheezing, chest tightness, dyspnea, and cough both immediately (immediate asthmatic response) and 4–6 hours later (late asthmatic response). Aspirin, other nonsteroidal anti-inflammatory drugs, sulfites added to foods and certain medications, beta-blockers, and other drugs (Table 9–24) can trigger attacks of asthma. Patients may present with chronic dry or nonproductive cough rather than with dyspnea and wheezing. In patients with this so-called "cough-variant asthma," baseline pulmonary function tests are normal but bronchial hyperreactivity can be demonstrated with bronchial provocation testing. Inhaled bronchodilators are often effective in controlling cough symptoms in these patients.

Physical findings vary with the severity of the attack. A mild attack may produce only slight tachycardia and tachypnea, with prolonged expiration and mild diffuse wheezing. More severe attacks are associated with use of accessory muscles of respiration, distant breath sounds, loud wheezing, hyperresonance, and intercostal retraction. Ominous signs in severe asthma include[1] fatigue,[2] pulsus paradoxus (> 20 mm Hg),[3] diaphoresis,[4] inaudible breath sounds with diminished wheezing,[5] inability to maintain recumbency,[6] and cyanosis.

B. Laboratory Findings: The total white blood cell count may be slightly increased during an acute attack, and eosinophilia is common. Expectorated sputum is viscid on gross examination; microscopic findings include mucus casts of small airways (Curschmann's spirals), eosinophils, and elongated rhomboid crystals derived from eosinophil cytoplasm (Charcot-Leyden crystals). Pulmonary function tests (Table 9–2) reveal abnormalities typical of obstructive dysfunction, and partial reversibility (improvement in FVC or FEV_1 of at least 15% or improvement in FEF_{25-75} of at least 25%) is often demonstrated after an inhaled bronchodilator is administered. It is important to emphasize that the absence of improvement in the pulmonary function test after bronchodilator does not constitute proof of irreversible airflow obstruction. Measuring the peak expiratory flow rate (PEFR) with a simple, inexpensive hand-held device can also indicate the severity of airflow limitation. Predicted values for PEFR vary with sex, age, and height, and are typically 450–650 L/min in men and 350–500 L/min in women. Values under 100–200 L/min indicate severe ventilatory dysfunction.

Arterial blood gas measurements in asthma may be normal during a mild attack, but respiratory alkalosis and mild hypoxemia are usually observed. In more severe cases, hypoxemia worsens and respiratory alkalosis disappears when respiratory muscle fatigue prevents hyperventilation. Normalization of the P_{CO_2} or development of respiratory acidosis in this circumstance may indicate the need for mechanical ventilation.

C. Imaging: Routin chest radiographs in adults and children with uncomplicated attacks re-

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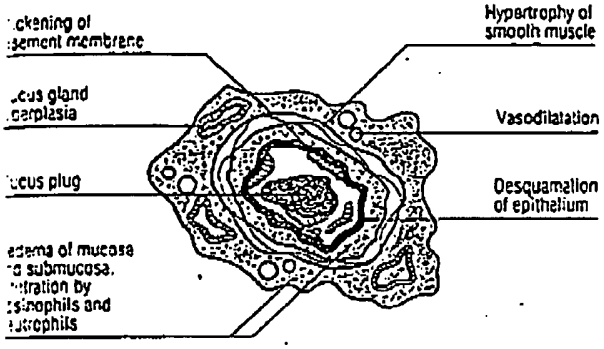

Fig. 15.31 The pathology of asthma
Intense inflammation, with oedema and intraluminal mucous plugs, is the striking pathology of asthma.

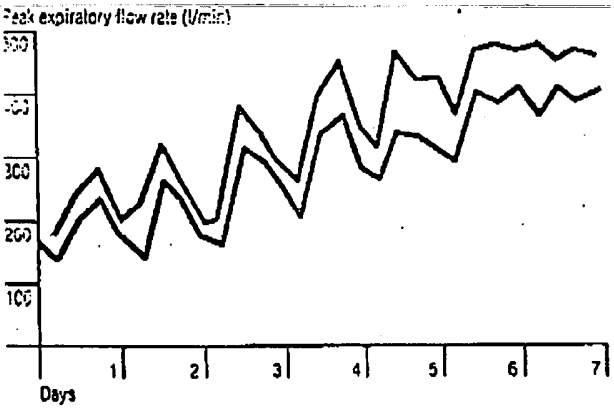

Fig. 15.32 Peak expiratory flow rate (PEFR) in asthma
The measurement of peak flow is essential for the management of asthma. PEFR is [illegible] in asthmatics; it is lowest in the early hours of the morning and on wakening (morning dipping) and increases with β2 agonists (e.g. salbutamol). The chart is typical of a patient recovering from an episode of moderately severe asthma.

When the inflammation in the airway wall is persistent or untreated and the asthma is symptomatically unremitting and severe, new pathological changes occur in the airway wall. There is bronchial smooth muscle hypertrophy with subepithelial fibrosis which may lead to fixed airflow obstruction that is unresponsive to inhaled bronchodilators.

In chronic asthma, particularly that which has persisted from childhood, there may be chest wall deformity. When asthma is severe the patient is distressed and vigorously contracting the accessory muscles of respiration. When the condition progresses despite active treatment, the patient is then said to have *'acute severe asthma'* (p. 545).

A number of clinical conditions are associated with asthma (Table 15.24). *Allergic bronchopulmonary aspergillosis* and other eosinophilic syndromes are discussed on page 546.

Table 15.24 Clinical syndromes associated with asthma

- Eosinophilic syndromes
  - Allergic bronchopulmonary aspergillosis
  - Idiopathic pulmonary eosinophilia
  - Tropical eosinophilia
  - Churg–Strauss syndrome
- Aspirin sensitivity and nasal polyposis
- Pericarditis
- Carcinoid syndrome

Investigation

X-ray findings

Most asthmatics have normal or hyperinflated lungs on chest X-ray. Mucus plugs can cause focal or segmental atelectasis, and sometimes collapse of a lobe or lung. Transient infiltrates are seen in association with eosinophilia. Spontaneous pneumothorax can complicate asthma in the acute phase.

Other investigations

Blood eosinophilia is common; it is usually greater in atopic asthma. Skin prick tests to common allergens may occasionally reveal an unsuspected source of allergy.

Lung function tests may be normal between attacks. During episodes of asthma the PEFR, FEV_1 and FEV_1/VC ratio will be reduced and airways resistance increased.

In addition to airflow obstruction the patient with acute or chronic asthma will have laboratory evidence of *hyperinflation* with increased total lung capacity (TLC), residual volume (RV), and ratio of RV to TLC. The *transfer factor* (diffusing capacity) for carbon monoxide is normal or increased in uncomplicated asthma. Hypoxaemia is common.

Diagnosis and management

Recognition of asthma is not always straightforward. It is often not recognised in children who present with episodes of cough, wheeze and dyspnoea. Such 'wheezy bronchitis' in childhood is almost always asthma. The differential diagnosis of chronic asthma includes: 'asthmatic' bronchitis, left heart failure, centrally obstructing tumour or foreign body and recurrent pulmonary emboli. It may be difficult or impossible to distinguish late-onset asthma from chronic obstructive bronchitis in the elderly smoker. Many of them respond well to bronchodilators and have a better prognosis than patients with fixed airways obstruction.

Asth. bronch.

Supervision of chronic asthma is as important as in any serious chronic condition. Some hospitals run a very effective 'open-door' policy for asthmatics, allowing them to obtain immediate specialist advice whenever their asthma is severe.

Education about the nature of the disease, the use of drugs and delivery systems, the avoidance of allergens and the recognition of deteriorating asthma are all important. Asthma

1948 1998

Annex 6

WORLD HEALTH ORGANIZATION PRESS OFFICE

PRESS

1211 GENEVA 27 SWITZERLAND · TELEPHONE: 791 2111 · CABLES: UNISANTE-GENEVE · TELEX: 415 416 · FAX: 791 0746

WHO WEB SITE: http://www.who.ch/

Press Release WHO/92
7 December 1998

EMBARGOED UNTIL 00h00 GMT OF 11 DECEMBER 1998

HELP OUR CHILDREN BREATHE

FIRST WORLD ASTHMA DAY LAUNCHED

There are between 100 and 150 million people in the world, including many children, who do not take breathing for granted. For them it can be a life-and-death struggle against recurrent attacks of breathlessness and wheezing caused by asthma. Each year, around 180 000 of these sufferers lose the battle and die of the disease.

To highlight the plight of asthma sufferers and raise public and professional awareness about this condition, the international community today launched World Asthma Day. The Day will be marked each 11 December under different themes. *"Help Our Children Breathe"* was chosen for the first World Asthma Day to emphasize the high incidence and gravity of the disease in children throughout the world.

"Asthma is a serious condition that affects the lives of millions of people in both developed and developing countries. Since the 1960s, the number of asthmatics has been steadily rising," said WHO expert, Dr Nikolai Khaltaev.

Today, an estimated 8% of the Swiss population suffers from asthma as against only 2% some 25-30 years ago. In Western Europe as a whole, asthma cases have doubled in the last 10 years, according to the UCB Institute of Allergy in Belgium. In the United States the number of asthmatics has leapt by over 60% since the early 1980s and deaths have reached 5 000 a year.

"Asthma is not just a public health problem for the developed countries," Dr Khaltaev emphsized. "India, for example, has an estimated 15 to 20 million asthmatics. However, in the developing world, the incidence of asthma varies greatly: from over 50% among children in the Caroline Islands to virtually zero in Papua New Guinea," he said.

"The prevalence of asthma in children can be as high as 30% in certain populations," explained Professor Romain Pauwels, Chairman of the Global Initiativ for Asthma (GINA). "In Australia, for example, one child in six under the age of 16 is affected today. Asthma is also the single most common chronic disease causing absence from school.

Annex 7 P1

WORLD HEALTH ORGANIZATION

FACT SHEET

WEBSITE: http://www.who.int

1211 GENEVA 27 SWITZERLAND - TELEPHONE: 791.21.11 - CABLES: UNISANTE-GENEVE - TELEX: 415.416 - FAX: 791.07.40 - E-MAIL: inf@who.int

WHO Fact Sheet N° 206
Revised January 2000

Page 1

BRONCHIAL ASTHMA

The Scale of the Problem: Between 100 and 150 million people around the globe -- roughly the equivalent of the population of the Russian Federation -- suffer from asthma and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually.

- Around 8% of the Swiss population suffers from asthma as against only 2% some 25-30 years ago.
- In Germany, there are an estimated 4 million asthmatics.
- In Western Europe as a whole, asthma has doubled in ten years, according to the UCB Institute of Allergy in Belgium.
- In the United States, the number of asthmatics has leapt by over 60% since the early 1980s and deaths have doubled to 5,000 a year.
- There are about 3 million asthmatics in Japan of whom 7% have severe and 30% have moderate asthma.
- In Australia, one child in six under the age of 16 is affected.

Asthma is not just a public health problem for developed countries. In developing countries, however, the incidence of the disease varies greatly.

- India has an estimated 15-20 million asthmatics.
- In the Western Pacific Region of WHO, the incidence varies from over 50% among children in the Caroline Islands to virtually zero in Papua New Guinea.
- In Brazil, Costa Rica, Panama, Peru and Uruguay, prevalence of asthma symptoms in children varies from 20% to 30%.
- In Kenya, it approaches 20%.
- In India, rough estimates indicate a prevalence of between 10% and 15% in 5-11 year old children.

The Human and Economic Burden: Mortality due to asthma is not comparable in size to the day-to-day effects of the disease. Although largely avoidable, asthma tends to occur in epidemics and affects young people. The human and economic burden associated with this

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condition is severe. The costs of asthma to society could be reduced to a large extent through concerted international and national action.

- Worldwide, the economic costs associated with asthma are estimated to exceed those of TB and HIV/AIDS combined.
- In the United States, for example, annual asthma care costs (direct and indirect) exceed US$6 billion.
- At present Britain spends about US$1.8 billion on health care for asthma and because of days lost through illness.
- In Australia, annual direct and indirect medical costs associated with asthma reach almost US$460 million.

What is Asthma? Asthma attacks all age groups but often starts in childhood. It is a disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. In an individual, they may occur from hour to hour and day to day.

This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs.

Causes: Asthma cannot be cured, but could be controlled. The strongest risk factors for developing asthma are exposure, especially in infancy, to indoor allergens (such as domestic mites in bedding, carpets and stuffed furniture, cats and cockroaches) and a family history of asthma or allergy. A study in the South Atlantic Island of Tristan da Cunha, where one in three of the 300 inhabitants has asthma, found children with asthmatic parents were much more likely to develop the condition.

Exposure to tobacco smoke and exposure to chemical irritants in the workplace are additional risk factors. Other risk factors include certain drugs (aspirin and other non-steroid anti-inflammatory drugs), low birth weight and respiratory infection. The weather (cold air), extreme emotional expression and physical exercise can exacerbate asthma.

Urbanization appears to be correlated with an increase in asthma. The nature of the risk is unclear because studies have not taken into account indoor allergens although these have been identified as significant risk factors.

Experts are struggling to understand why rates worldwide are, on average, rising by 50% every decade. And they are baffled by isolated incidents involving hundreds of people in a city, who suffer from allergies such as hay fever but who had never had asthma, suddenly being struck down by asthma attacks so severe they needed emergency hospital treatment.

- One such incident in London, UK, in June 1994 saw 640 people rushed to emergency departments in the throes of full-blown asthma attacks. A similar incident happened in Melbourne, Australia. Many experts have blamed climatic conditions such as thunderstorms, which break up pollen grains, releasing starch granules that trigger attacks. But they do not know why ordinary hay-fever sufferers developed a life-threatening condition without warning.

Treatment: Because asthma is a chronic condition, it usually requires continuous medical care. Patients with moderate to severe asthma have to take long-term medication daily (for example, anti-inflammatory drugs) to control the underlying inflammation and prevent symptoms and attacks. If symptoms occur, short-term medications (inhaled short-acting beta2-agonists) are used to relieve them.

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Fact Sheet N° 206

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Medication is not the only way to control asthma. It is also important to avoid asthma triggers -- stimuli that irritate and inflame the airways. Each person must learn what triggers he or she should avoid.

Although asthma does not kill on the scale of chronic obstructive pulmonary diseases (COPD), failure to use appropriate drugs or comply with treatment, coupled with an under-recognition of the severity of the problem, can lead to unnecessary deaths, most of which occur outside hospital.

The Way Forward and the Role of the WHO: WHO recognizes asthma as a disease of major public health importance and plays a unique role in the co-ordination of international efforts against the disease. International action is needed to:

- increase public awareness of the disease to make sure patients and health professionals recognize the disease and are aware of the severity of associated problems;
- organize and co-ordinate global epidemiological surveillance to monitor global and regional trends in asthma;
- develop and implement an optimal strategy for its management and prevention (many studies have shown that this will result in the control of asthma in most patients); and
- stimulate research into the causes of asthma to develop new control strategies and treatment techniques.

WHO Activities:

International Study of Asthma and Allergies in Childhood (ISAAC): WHO collaborates in ISAAC and, more particularly, in the implementation of the study in developing countries with areas of severe air pollution. A preliminary objective is to obtain information on the association between childhood asthma and air pollution. The first results of this study have shown the prevalence of asthma symptoms to vary from 1.6% to 36.8%.

Global Initiative for Asthma (GINA): In 1992, WHO and the US-based National Heart, Lung and Blood Institute jointly formed GINA to cut deaths and disability by developing and implementing an optimal strategy for asthma management and prevention. Since its inception GINA has:

- produced a report covering a range of information detailing all the latest knowledge on causes, the mechanism of the disease, risk factors, management, education and socio-economic factors;
- developed guidelines on asthma management for doctors, nurses, public health officials, patients and their families;
- held workshops to introduce the GINA programme to public health officials and medical professionals in more than 80 countries, leading to implementation of the guidelines;
- been active in disseminating information in 20 languages and bringing together organizations devoted to improving asthma care;
- backed research efforts to improve asthma management.

GINA's goal is to build an active network with multiple organizations concerned with asthma to ensure better patient car worldwide.

WHO Initiative on Allergic Rhinitis and Its Impact on Asthma (ARIA): WHO is developing a strategy for the prevention of bronchial asthma through the management of allergic rhinitis. The strategy was conceived by specialists from all over the world at a December 1999 meeting on ARIA.

Allergic rhinitis is defined as an allergen-induced inflammation of the membranes lining the nose. Based on the time of exposure to the allergen, allergic rhinitis can be subdivided into perennial, seasonal or occupational disease.

Three statements must be taken into account for the successful prevention of bronchial asthma:

- Among the broad spectrum of allergic diseases, bronchial asthma is the most prevalent, dangerous and life-threatening.
- Underestimated up to now, allergic rhinitis is an important risk factor for asthma.
- One efficient way to prevent bronchial asthma is to control and treat allergic rhinitis from the very beginning of its inception.

Generally speaking, ARIA will broaden the perspectives for primary prevention of bronchial asthma and will promote better understanding of bronchial asthma among physicians and patients.

The specific goals of ARIA are defined as follows :

- To increase awareness of allergy and allergic diseases as a preventable public health problem among the medical community, public health officials, and the general public;
- To prepare evidence-based guidelines for the prevention and management of allergic rhinitis as a key element of primary prevention of bronchial asthma;
- To educate physicians and other health care professionals about the relevance of allergic rhinitis to bronchial asthma; and
- To educate the public about the potentially fatal risks of allergy (anaphylaxis) and asthma, especially in children, and to encourage greater dialogue with their physicians. Better education and increased dialogue could avoid approximately 25,000 childhood deaths due to asthma each year.

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Page 1

II. Procedural Considerations Related to Rejections for Lack of Utility

A. The Claimed Invention is the Focus of the Utility Requirement

The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement. Each claim (i.e., each "invention"), therefore, must be evaluated on its own merits for compliance with all statutory requirements. Generally speaking, however, a dependent claim will define an invention that has utility if the claim from which it depends has defined an invention having utility.[29] Where an applicant has established utility for a species that falls within a identified genus of compounds and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under § 101.[30]

It is common and sensible for an applicant to identify several specific utilities for an invention, particularly where the invention is a product (e.g., a machine, an article of manufacture or a composition of matter). However, regardless of the category of invention that is claimed (e.g., product or process), an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy § 101 and § 112; additional statements of utility, even if not "credible" do not render the claimed invention lacking in utility.[31] Thus, if applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established.

Statements made by the applicant in the specification or incident to prosecution of the application before the Office cannot, standing alone, be the basis for a "lack of utility" rejection under § 101 or § 112.[32] An applicant may include statements in the specification whose technical accuracy cannot be easily confirmed if those statements are not necessary to support the patentability of an invention with regard to any statutory basis. Thus, the Office should not require an applicant to strike non-essential statements relating to utility from a patent disclosure, regardless of the technical accuracy of the statement or assertion it presents. Office personnel should also be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention.[33] Doing so can inappropriately change the relationship of an asserted utility to the claimed invention and raise issues not relevant to examination of that claim.

B. Is There an Asserted or Well-Established Utility for the Claimed Invention?

Upon initial examination, the Examiner should review the specification to determine if there are any statements asserting that the claimed invention is useful for any particular purpose. A complete disclosure should include a statement which identifies a specific utility for the invention.

1. An Asserted Utility Must Be Specific, Not General

A statement of specific utility should fully and clearly explain why the applicant believes the invention is useful. Such statements will usually explain the purpose of or how the invention may be used (e.g., a compound is believed to be useful in the treatment of a particular disorder). Regardless of the form of statement of specific utility, it must enable one ordinarily skilled in the art to understand why the applicant believes the claimed invention is useful.

Except where an invention has a well-established utility, the failure of an applicant to specifically identify why an invention is believed to be useful renders the claimed invention deficient under § 101 and § 112, first paragraph. In such cases, the applicant has failed to identify a "specific utility" for the claimed invention. For

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II. Special C nsiderations for Asserted Therapeutic or Pharm cological Utilities

The Federal courts have consistently reversed rejections by the Office asserting a lack of utility for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence that reasonably supports such a utility. In view of this, Office personnel should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility.

A. A Reasonable Correlation Between the Evidence and the Asserted Utility is Sufficient

As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility.[55] An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use.[56]

B. Structural Similarity to Compounds with Established Utility

Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound.[57] Such evidence should be given appropriate weight in determining whether one skilled in the art would find the asserted utility credible. Office personnel should evaluate not only the existence of the structural relationship, but also the reasoning used by the applicant or a declarant to explain why that structural similarity is believed to be relevant to the applicant's assertion of utility.

C. Data from In Vitro or Animal Testing is Generally Sufficient to Support Therapeutic Utility

If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.[58] In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials.

If an applicant provides data, whether from in vitro assays or animal tests or both, to support an asserted utility, and an explanation of why that data supports the asserted utility, the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility.[59] Office personnel must be careful to evaluate all factors that might influence the conclusions of a person of ordinary skill in the art as to this question, including the test parameters, choice of animal, relationship of the activity to the particular disorder to be treated, characteristics of the compound or composition, relative significance of the data provided and, most importantly, the explanation offered by the applicant as t why the information provided is believed to support the asserted utility. If the data supplied is consistent with the asserted utility, the Office cannot

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maintain a rejection under § 101.

Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted utility. Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility.[60] Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application.[61]

D. Human Clinical Data

Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders,[62] even with respect to situations where no art-recognized animal models exist for the human disease encompassed by the claims.[63] Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

E. Safety and Efficacy Considerations

The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the Government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs.[64] As the Federal Circuit recently held, "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws."[65]

Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness.[66]

F. Treatment of Specific Disease Conditions

Claims directed to a method of treating or curing a disease for which there have been no previously successful treatments or cures warrant careful review for compliance with § 101.[67] The fact that there is no known cure for a disease, however, cannot serve as the basis for a conclusion that such an invention lacks utility. Rather, Office personnel must determine if the asserted utility for the

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invention is credible based on the information disclosed in the application. Only those claims for which an asserted utility is not credible should be rejected.

In such cases, the Office should carefully review what is being claimed by the applicant. An assertion that the claimed invention is useful in treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support. In contrast, an assertion that the claimed invention will be useful in "curing" the disease may require a significantly greater amount of evidentiary support to be considered credible by a person of ordinary skill in the art.[68]

It is important to note that the Food and Drug Administration has promulgated regulations that enable a party to conduct clinical trials for drugs used to treat life threatening and severely-debilitating illnesses, even where no alternative therapy exists.[69] Implicit in these regulations is the recognition that experts qualified to evaluate the effectiveness of therapeutics can and often do find a sufficient basis to conduct clinical trials of drugs for "incurable" or previously untreatable illnesses. Thus, affidavit evidence from experts in the art indicating that there is a reasonable expectation of success, supported by sound reasoning, usually should be sufficient to establish that such a utility is credible.

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Pharmaceuticals, Kenilworth, N.J.) for at least two months. Thirty-five subjects were taking oral prednisone at a dose of no more than 20 mg daily or 40 mg every other day in addition to the inhaled corticosteroids. Criteria for eligibility included positive responses on skin-prick testing to two or more perennial allergens to which the subjects would be exposed and documented reversibility of the airway abnormalities (an increase of 12 percent or more after the administration of albuterol). In the week before randomization the subjects also had to have an FEV_1 that was 50 to 90 percent of the predicted value and a mean symptom score of at least 2.5 on each of the seven days.

The most common reasons for exclusion were a daily symptom score of less than 2.5 (26 percent of those excluded), airway obstruction that was not reversible (13 percent), a dose of rhuMAb-E25 that was projected to be less than 1 ml (11 percent), scheduling problems (10 percent), a serum IgE concentration of more than 1785 IU per milliliter (9 percent), negative skin-prick tests (8 percent), an FEV_1 that was outside the specified range (7 percent), active disease other than asthma (7 percent), and lack of compliance (5 percent).

Study Design

This randomized, placebo-controlled, double-blind, multicenter trial comprised four phases: a 4-week enrollment and run-in period; 12 weeks of adjunctive treatment in which placebo or rhuMAb-E25 was administered intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter, in addition to established corticosteroid therapy; an 8-week phase in which rhuMAb-E25 or placebo was continued but the doses of corticosteroids were tapered; and a 10-week follow-up phase. Subjects who were randomly assigned to receive rhuMAb-E25 were given either a high dose (5.8 μg per kilogram of body weight per nanogram of IgE per milliliter) or a low dose (2.5 μg per kilogram per nanogram of IgE per milliliter).

Outcome Measures

The primary outcomes were daytime and nocturnal asthma symptom scores at 12 weeks. The secondary outcomes were changes in the extent of use of a β-agonist bronchodilator as a rescue medication, the doses of oral and inhaled corticosteroids, peak expiratory flow rate, and asthma-specific quality of life. The safety and tolerability of rhuMAb-E25 were evaluated.

Serum concentrations of free and total IgE were measured by an enzyme-linked immunoassay[8,10] with the use of Fc-receptor–IgG chimeric antibody and monoclonal anti-IgE.

Asthma Symptom Scores

Symptoms of asthma were recorded twice daily with use of an electronic diary[11] (MiniDoc Electronic Patient System, *MiniDoc*, Northbrook, Ill.). Separate scales were used for adults and adolescents (age, 11 to 17 years). Adults used the following scale to rate their symptoms in the preceding 24 hours: none, a score of 1; very little, a score of 2; some, a score of 3; a moderate amount, a score of 4; a good deal, a score of 5; a great deal, a score of 6; and a very great deal, a score of 7. The frequency of symptoms in the preceding 24 hours was scored with use of the following scale: none of the time, a score of 1; hardly any of the time, a score of 2; a little of the time, a score of 3; some of the time, a score of 4; a good bit of the time, a score of 5; most of the time, a score of 6; and all of the time, a score of 7. The total symptom score for adults was the average score for 9 questions regarding magnitude and 7 regarding frequency on a given day (3 questions in the morning and 13 in the evening).

The scale used by adolescents to assess the magnitude of their symptoms was similar to that used by adults, but it used simplified language: a score of 1 indicated that they were not bothered by symptoms, a score of 2 hardly bothered, a score of 3 bothered slightly, a score of 4 somewhat bothered, a score of 5 quite bothered, a score of 6 very bothered, and a score of 7 extremely bothered. Adolescents used essentially the same scale as adults to assess the frequency of symptoms. The total symptom score for adolescents was the average score for 9 questions regarding magnitude and 8 regarding frequency on a given day (3 questions in the morning and 14 in the evening).

The percent reduction in the symptom score was calculated according to the following formula: (base-line score − follow-up score) ÷ (base-line score − 1), where the base-line score is the mean symptom score for the week before day 0 and the follow-up score is the mean symptom score on week 12 or week 20.

Use of Inhaled β-Agonists and Withdrawal of Corticosteroids

The extent of use of inhaled β-agonists was recorded in the electronic diary twice daily. A total of 315 subjects used β-agonists as rescue therapy, and 202 used metered-dose inhalers exclusively. Results are presented only for the 202 subjects who used metered-dose inhalers exclusively. After 12 weeks of treatment with rhuMAb-E25 or placebo, subjects began the third phase (withdrawal of corticosteroids). Treatment with rhuMAb-E25 or placebo was continued during this phase. Every two weeks during this eight-week period, the subjects underwent a physical examination and had their FEV_1 and peak expiratory flow rate measured, their diary cards assessed, and their total use of rescue medication and corticosteroids evaluated. For subjects who required high daily doses of inhaled triamcinolone (>600 μg per day), an attempt was made to reduce the dose by 200 μg every two weeks; for subjects who were taking less than 600 μg per day, the target reduction in the dose was 25 percent of the base-line value every two weeks. Weekly decreases were not permitted. For subjects who were taking no more than 20 mg of oral corticosteroids daily or 40 mg every other day, the dose was reduced by no more than 20 percent at one-week intervals. For subjects who were taking both oral and inhaled corticosteroids, only the dose of the oral agent was tapered.

Measurements of Lung Function

FEV_1 was measured every two weeks.[12] Peak expiratory flow rates were measured in the morning and evening by the subjects with a portable peak-flow meter (Mini-Wright flowmeter, Armstrong Industries, Northbrook, Ill.).

Assessment of the Quality of Life

A total of 263 adults completed the Asthma Quality-of-Life Questionnaire[13] and 45 adolescents completed the Pediatric Asthma Quality-of-Life Questionnaire[14] at base line, week 12, and week 20. The adult questionnaire that we used is a validated, asthma-specific instrument.[13] Subjects rate the degree of impairment caused by asthma during the preceding 14 days and respond to each of the 32 items using a 7-point scale on which a score of 1 indicates maximal impairment and a score of 7 no impairment. Changes in the score of 0.5, 1.0, and 1.5 correspond to small, moderate, and large differences, respectively.[15] The questionnaire can be used to provide an overall score and scores in four areas: limitation of activities, asthma symptoms, emotional functioning, and symptoms arising from environmental exposures.

The pediatric questionnaire was designed and validated for use in children with asthma who are 7 to 17 years of age.[14] It has 23 items covering three areas (symptoms, limitation of activities, and emotional functioning). The scoring system is identical to that of the adult questionnaire.

Exacerbations of Asthma

If an exacerbation of asthma occurred during the withdrawal of corticosteroids, the tapering was interrupted and the exacerbation was treated with prednisone for five to seven days. An exacerbation was defined by any of the following: a decrease in morning peak expiratory flow rate of at least 20 percent during three of the seven days preceding a visit, a decrease in FEV_1 of at least 20 percent, an urgent or unscheduled visit for asthma symptoms, or

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Asthma symptoms score	Patients treated with glycophosphopeptical N=55	Patients treated with Nigella Sativa N=60	Paticnts treated with placebo N=35
Base linc (day 1) Mean+SEM	34.2+ 0.42	33.39+ 0.3	33.2+ 0.52
P-values are fore the comparison with placebo	P<0.01	N.S	
P-valve for comparison between glycophosphopeptical and Nigella Sativa	P<0.01		
Day (3) Mean + SEM	20.54 +0.71	17.99 +1.2	27.3 + 1.19
P-value for comparison between glycophosphopeptical and Nigella Sativa	N.S		
Day (7) Mcan + SEM	9.65 +0.99	9.71 +0.94	29.7 +0.99
P-values are for the comparison with placebo	P>0.001	P>0.001	
P-value for comparison between glycophosphopeptical and Nigella Sativa	N.S		
Day (14) Mean + SEM	5.8 +0.84	6.55 +0.7	30.62 +0.91
P-values are for the comparison with placebo	P>0.001	P>0.001	
P-value for comparison between glycophosphopeptical and Nigella Sativa	N.S		
Day (21) Mean + SEM	4.38 +0.9	5.82 +0.71	31.43 +0.66
P-values are for the comparison with placebo	P>0.001	P>0.001	
P-valuc for comparison between glycophosphopeptical and Nigella Sativa	N.S		

Table -1- Reduction in over all asthma symptoms scores.

UNITED STATES PATENT AND TRADEMARK OFFICE

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UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/944,564	09/04/2001	Nida Abdul-Ghani Nassief	

CONFIRMATION NO. 8476

OC000000008175372

AL-JASSIM, Rawaa
2578 River Woods Drive
Naperville, IL 60565

Title: Asthma/allergy therapy that targets T-lymphocytes and/or eosinophils

Publication No. US-2002-0061841-A1
Publication Date: 05/23/2002

Date Mailed: 05/23/2002

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